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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

June 17, 1980

OFFICE OF TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Special Review of Data Requirements for 2,4-D

FROM: Dr. H. Wade Fowler, Jr.
Executive Secretary
FIFRA Scientific Advisory Panel

H. Wade Fowler, Jr.

TO: Deputy Assistant Administrator
for Pesticide Programs

The FIFRA Scientific Advisory Panel completed a special review of possible data gaps with 2,4-D to determine test requirements needed to support continued registration of the pesticide. The review was completed in an open meeting of the Panel held in Arlington, Virginia, on May 28, 1980.

Attached is a report of findings by the Panel.

Attachment

cc: Mr. Conlon
Dr. McGrath
Ms. Anita Schmidt
Panel Members

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

SCIENTIFIC ADVISORY PANEL

Special Review of Data Requirements for 2,4-D

The FIFRA Scientific Advisory Panel completed a special review of possible data gaps with 2,4-D to determine test requirements needed to support continued registration of the pesticide. The review was completed in an open meeting of the Panel held in Arlington, Virginia, on May 28, 1980.

Maximum public participation is encouraged at all meetings of the Scientific Advisory Panel. In respect to this session, the meeting was announced in the Federal Register on May 12, 1980. In addition, the secretariat of the Panel routinely sends telephonic notices and special mailings to members of the general public who have indicated an interest in activities of the Panel.

Written and oral statements were received from Dr. Dieter Riedel of the Occupational Toxicology Division, Environment Health Directorate of Canada; the National Forest Products Association; and from technical staff of the Environmental Protection Agency.

The excellent briefings by Mr. Johnson, Deputy Assistant Administrator for Pesticide Programs (OPP), in company with Ms. Anne Barton, Ms. Anita Schmidt and Dr. Henry Spencer of his staff, were of great value to members of the Panel.

In consideration of all matters brought out during the meeting, the Panel unanimously submits the following report in response to specific proposals by the Agency for certification of test requirements involving studies on oncogenicity; reproductive effects; mutagenicity; metabolism; neurotoxicity; acute toxicity; and dermal absorption:

ONCOGENICITY

Test Requirements under Review by the Agency:

1. Standard oral exposure studies of acid in rats and mice.

2. A subcutaneous or dermal exposure study of isooctyl ester in mice.

PANEL COMMENTS:

The agency has suggested three oncogenicity studies in the list of proposed data requirements for 2,4-D: (1) standard oral exposure studies of acid in rats; (2) in mice; and (3) a subcutaneous or dermal exposure study of the isooctyl ester in mice. The FIFRA Scientific Advisory Panel concurs with the need for a cancer bioassay study in mice since neither the Innes et al. nor the Archipov and Kozlova studies provide sufficient information to make a meaningful scientific judgment. The Scientific Advisory Panel has noted previously the difficulty of using data from the Innes et al. study as the basis for evaluating oncogenicity in mice and would urge the Agency to avoid using data from this study for either a positive or negative determination of oncogenicity for any of the agents included in this study.

The FIFRA Scientific Advisory Panel does not concur with the Agency suggestion for a subcutaneous or dermal exposure study of the isooctyl ester of 2,4-D in mice for several reasons. First, oncogenicity bioassays using the subcutaneous or dermal routes of exposure are generally less reliable than the standard oral test in predicting oncogenicity in any species. Second, the basis for this requirement appears to be a peripheral study which was added to the Innes et al. study on 2,4-D and which has serious defects (single sex, single dose, questionable controls, etc.) in addition to those generally associated with the Innes et al. protocol and evaluation. As indicated above, the FIFRA Scientific Advisory Panel recommends against the use of data from this study for oncogenicity evaluation of any of the agents included in the tests.

The FIFRA Scientific Advisory Panel has reviewed the chronic toxicity study on 2,4-D carried out in rats and dogs by Hansen et al. which was published in Toxicology and Applied Pharmacology (TAP). In addition to peer review of this study by the editor and editorial board of TAP, the study has also been reviewed by the National Cancer Institute (NCI) and by Dr. M. Rueber. The NCI review agreed with the conclusion of the authors of this paper that a carcinogenic effect was not demonstrated for 2,4-D whereas Dr. Rueber's conclusion was that 2,4-D is carcinogenic in male and female rats and probably also in mice. In Dr. Rueber's report, he agreed (page 5) that this FDA study (Hansen et el.) must be considered as an acceptable study, and thus the major difference in the conclusions of Dr. Rueber and the authors of this study derives primarily

from differences in the interpretation and evaluation of the rat histopathologic data. Dr. Rueber agrees with the authors of the FDA study that 2,4-D was not shown to be carcinogenic in dogs but argues that two years is an insufficient study period to detect carcinogensis in this species. It should be pointed out that carcinogenic effects have been produced in dogs in studies of less than 2 years duration and the 2-year period is the recommended exposure period in the current FIFRA guidelines for chronic toxicity studies in dogs. The FIFRA Scientific Advisory Panel recommends that the Agency attempt to resolve the apparent controversy between Dr. Rueber's pathologic interpretation of the rat histologic findings and those of the authors of the FDA study before requesting any additional oncogenicity testing in rats with 2,4-D.

In connection with the issue of additional oncogenicity testing with 2,4-D in rats, the FIFRA Scientific Advisory Panel wishes to remind the Agency that it is virtually impossible to carry out a chronic toxicity study that is totally without flaws. The decision of whether these flaws are inconsequential or whether they render the study useless for toxicologic evaluation depends both on the judgment and experience of the evaluator and on the rest of the information contained in the toxicity data base. Thus, the existence of "data gaps" and "inadequate studies" in a toxicity data base for a compound does not a priori preclude a toxicologic evaluation of the compound, although it should increase the "uncertainty factor" or safety factor associated with any such predictive effort. The FIFRA Scientific Advisory Panel supports the efforts of the Agency to improve the quality of the toxicity data base through mechanisms such as the identification of "data gaps", the development of guidelines for toxicity testing protocols, and the RPAR process, but it is equally aware of the fact that the requirement of additional animal studies which are not clearly justified will waste resources which are already in short supply and damage Agency credibility.

It is recommended, therefore, that in establishing requirements for additional toxicity studies the Agency distinguish between those requirements which it considers to be essential (need to know) and those which it considers to be desirable (nice to know). This priority ranking should also provide an indication of the urgency associated with the requirement for additional testing. This approach would provide the Agency with greater flexibility in dealing with the older pesticides (like 2,4-D) which have a relatively good "track record" in terms of producing adverse effects on human health and the environment.

SUMMARY OF PANEL COMMENTS:

The Panel is of the opinion that the Agency should resolve the controversy between the study conducted by Hansen et al, 1971 and the pathologic interpretation of that study by Reuber 1979 prior to certification that additional oncogenicity studies are required. In the event the results of the oncogenicity studies of Hansen et al. 1971 are validated as a result of examination of the appropriate slides related to lymphosarcoma in female rats, then the Panel would recommend that the testing requirement be limited to a standard oral exposure study in mice. In the event the results of the report by Hansen et al, 1971 are not validated on reexamination of tissue specimens, then an oral exposure study in both rats and mice is recommended.

REPRODUCTION

Test Requirements under Review by the Agency:

1. A multigeneration study to establish NOELS for the acid form of 2,4-D in one species.

2. Teratology/fetotoxicity studies to establish NOELS in rats for:

   a. Acid

   b. Butoxy Propyl Ester

   c. Alkanol Amine

   d. Isopropyl Ester

   e. Dichlorophenol metabolite

PANEL COMMENTS:

The Panel is of the opinion that an additional multigeneration study to establish NOELS for the acid form of 2,4-D in one species is not warranted. Although the Hansen et al study had some discrepancies, it still represents an adequate study of the potential reproductive hazard of 2,4-D. The study shows a statistically significant effect at 1500 ppm. However, except for the F_{1a} generation, 500 ppm and 100 ppm of 2,4-D do not cause any reproductive anomalies. In our opinion 500 ppm should be considered as a no observed effect level (NOEL) for reproductive toxicity in rats exposed to 2,4-D, and should be used in estimating the potential reproductive toxicity of 2,4-D to humans exposed to this compound.

The Panel concurs that teratology/fetotoxicity studies to establish NOELS in rats should be conducted in all the proposed data requirement areas.

MUTAGENICITY

Test Requirements under Review by the Agency:

None.

PANEL COMMENTS:

The Panel concurs with the appraisal by the Agency.

METABOLISM

Test Requirements under Review:

1. Standard metabolism studies in dogs and rats for acid, isooctyl ester and PGBE.

2. A standard metabolism study in pregnant rats for acid, isooctyl ester, and PGBE.

PANEL COMMENTS:

The Panel agrees with the appraisal by the Agency for standard metabolism studies in dogs and rats for acid, isooctyl ester, and PGBE. However, the Panel is of the opinion that standard metabolism studies in pregnant rats should not be done.

NEUROTOXICITY

Test Requirements under Review by the Agency:

1. Subchronic neurotoxicity studies in dogs, rats, and chickens by oral route (including a recovery period) for acid and dimethylamine.

2. A subacute dermal neurotoxicity study in dogs.

PANEL COMMENTS:

The Panel agrees that subchronic neurotoxicity studies in dogs, cats, rats, and chickens by the oral route (including a recovery period) for acid and dimethylamine should be conducted. However, the Panel is of the opinion that the subacute dermal neurotoxicity study in dogs should be delayed or not conducted.

ACUTE TOXICITY

Test Requirements under Rev w by the Agency:

1. Oral LD_{50} in rats r each formulation.

2. Dermal LD_{50} in rat for each formulation.

PANEL COMMENTS:

The Panel concurs with e appraisal by the Agency for acute toxicity data.

ERMAL ABSORPTION

Test Requirements under Rev w by the Agency:

A radiolabeled dermal absor ion study in an appropriate species for each formulation meeting th following criteria:

1. It contains an act e ingredient which has shown fetotoxic effects at relativ y low doses (this includes all 2,4-D forms included in e teratology study request plus the isooctyl ester and PGBE).

2. Its use is likely result in dermal exposure to human females.

PANEL COMMENTS:

The Panel concurs with he appraisal by the Agency for dermal absorption data.

ISH AND WILDLIFE

SPECIAL PANEL COMMENTS:

The Panel is concerned bout the potential adverse effects of 2,4-D to fish and wildlife. The nel notes a potentially serious data gap in this vital area and resp tfully requests that the Agency review the matter and present a re rt on possible studies to be conducted at a future meeting of the nel.

Selected References:

1. ARCHIPOV, G. N. and I. . Kozlova. 1974. Study of the carcinogenic properties of the her icide amine salt of 2,4-D. Voprosy Pitaniya 5:83-84.
2. HANSEN, W. H., M.L. Qua fe, R.T. Habermann and O.G. Fitzhugh. 1971. Chronic toxicity of 2 -dichlorophenoxyacetic acid in rats. Toxicol. Appl. Pharma ol. 20:122-129.

3. INNES, J.R.M., B.M. Ulland, M.G. Valerio, L. Petrucelli, L. Fishbein, E.R. Hart, A.J. Pallotta, R.R. Bates, H.L. Falk, J..J. Gart, M. Klein, I. Mitchell and J. Peters. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. J. Nat. Cancer Inst. 42:1101-1114.
4. REUBER, M.D. Carcinogenicity of 2,4-dichlorophenoxyacetic acid. June 12, 1979. Unpublished manuscript.

FOR THE CHAIRMAN:

H. Wade Fowler Jr.

H. Wade Fowler, Jr., Ph.D.
Executive Secretary
FIFRA Scientific Advisory Panel

DATE: June 13, 1980